Cell Metabolism
Previews

NRG4: An Endocrine Link between Brown Adipose Tissue and Liver

Alexander Pfeifer[1,*]
[1]Institute of Pharmacology and Toxicology, University of Bonn, 53127 Bonn, Germany
*Correspondence: alexander.pfeifer@uni-bonn.de
http://dx.doi.org/10.1016/j.cmet.2014.12.008

Brown adipose tissue (BAT) directly regulates energy homeostasis via uncoupling of mitochondrial ATP production and thermogenesis. Wang et al. (2014) now report that BAT controls liver lipogenesis via secretion of the growth factor NRG4.

Brown adipose tissue (BAT) is a special type of fat that dissipates energy in response to cold (Figure 1A), a process also known as nonshivering thermogenesis (Cannon and Nedergaard, 2004; Pfeifer and Hoffmann, 2014; Rosen and Spiegelman, 2014). In contrast, white adipose tissue (WAT) is the main site of energy storage in our body. BAT-dependent thermogenesis relies on the expression of uncoupling protein-1 (UCP-1), which is only expressed in brown adipocytes and uncouples mitochondrial fuel oxidation from ATP production resulting in heat production (Figure 1A). Although the importance of BAT for newborns is well-established, its role in human adults has remained elusive until recent imaging studies clearly revealed the presence of metabolically active BAT in human adults (Pfeifer and Hoffmann, 2014). The major focus of BAT research has been on UCP-1-mediated energy expenditure, though BAT is also thought to regulate whole-body metabolism through endocrine factors (Figure 1A) similar to WAT, which has long been recognized as an endocrine organ secreting adipokines (Villarroya et al., 2013). BAT-derived autocrine and/or paracrine signals (Figure 1A) include adenosine (Gnad et al., 2014) and nitric oxide (NO) (Nisoli et al., 1998). Moreover, BAT secretes endocrine factors, such as the thyroid hormone triiodothyronine (Silva and Larsen, 1985). Wang et al. (2014) now show that BAT controls de novo liver lipid synthesis via Neuregulin 4 (Nrg4).

Nrg4 is member of the epidermal growth factor (EGF) family expressed in murine lung, heart, and adipose tissues, with highest expression levels in BAT. Nrg4 contains an EGF-like domain that is released after proteolytic cleavage and acts as autocrine/paracrine or endocrine signal. A recent study (Rosell et al., 2014) independently identified Nrg4 to be enriched in BAT and in inducible brown adipocytes, also known as beige or brite cells (Pfeifer and Hoffmann, 2014; Rosen and Spiegelman, 2014).

To identify signaling molecules released from BAT, Wang et al. (2014) performed a secretome analysis across 12 mouse tissues and identified a cluster of 26 genes enriched in BAT and induced during brown adipocyte differentiation including *Nrg4*. To determine the target tissue of Nrg4, Wang et al. (2014) performed binding assays on sections of BAT, heart, muscle, liver, and spleen and found that Nrg4 binding was restricted to the liver, though the reason for this specificity remains unclear. Heterotopic expression and binding assays indicated that Nrg4 may signal via ErbB3 and ErbB4, which belong to the family of ErbB/HER protein-tyrosine kinase receptors (Figure 1B). To study Nrg4 function in vivo, Wang et al. (2014) generated Nrg4-deficient ($Nrg4^{-/-}$) mice. High-fat-fed $Nrg4^{-/-}$ mice exhibited a significant increase in body weight as well as an exacerbation of insulin resistance and fatty liver (i.e., hepatic steatosis). $Nrg4^{-/-}$ livers showed significantly higher expression of several genes involved in de novo lipogenesis (Figure 1B), which may account for the predisposition of $Nrg4^{-/-}$ mice to diet-induced hepatic steatosis. In stark contrast, mice overexpressing *Nrg4* in all adipose tissues gained significantly less weight than controls upon high-fat diet feeding and exhibited improved glucose tolerance and increased insulin sensitivity, together with significantly reduced hepatic steatosis and hepatic expression of lipogenic genes. Analysis of human WAT samples revealed that *NRG4* mRNA levels inversely correlated with body fat mass and liver fat content. Based on human and murine data, the authors speculate that reduced Nrg4 expression may be causally linked to the pathogenesis of nonalcoholic fatty liver disease (NAFLD). Because of the obesity pandemic, fatty liver also known as NAFLD has become the most common cause of chronic liver disease. It may be possible that BAT counteracts NAFLD in a 2-fold way: via secretion of Nrg4 to inhibit hepatic de novo lipogenesis and through the enormous capacity of activated BAT to clear nutrient lipids (Bartelt et al., 2011) and shift lipid flux away from the liver.

Several questions remain open regarding the therapeutic relevance of the reported findings. First, it will be important to determine whether human adipocytes secrete Nrg4 and how this might be regulated. Additionally, the mechanism of Nrg4 induction in adipocytes is not fully understood in mice and will require further investigation. It remains to be shown that Nrg4 signaling is restricted to the liver in humans as well. Given the wide-spread expression of ErbB3 and ErbB4 in humans (http://www.proteinatlas.org), Nrg4 might target also other tissues. Rosell et al. (2014) recently showed that conditioned medium from brown adipocytes induces neurite outgrowth in a rat neuronal cell line expressing ErbB4. This effect was Nrg4 dependent, suggesting that adipocyte-derived Nrg4 might also be involved in the control of the sympathetic neurons activating brown adipocytes. Thus, Nrg4 appears to be involved in a crosstalk between

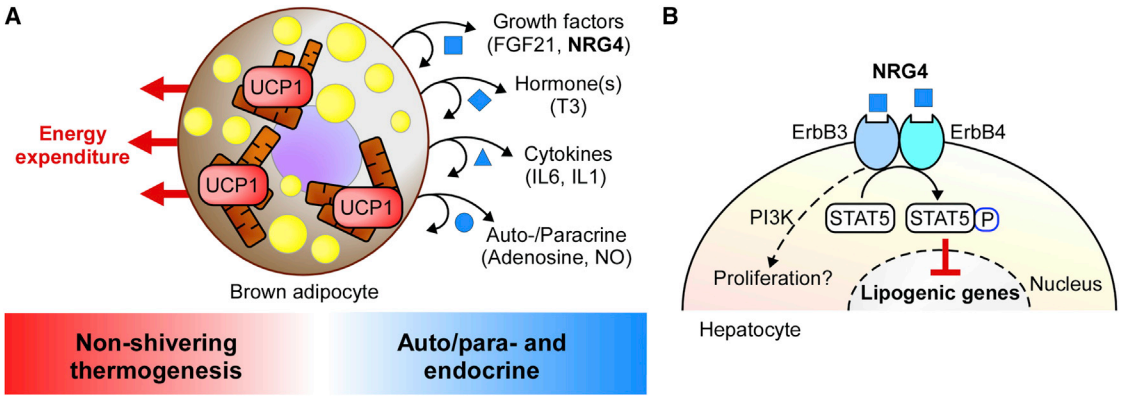

Figure 1. BAT Dissipates Energy and Secretes Signaling Molecules Like Nrg4, which Regulates Liver Lipid Metabolism

(A) BAT dissipates energy in response to cold via an UCP-1-dependent mechanism (left). BAT secretes also a variety of signaling molecules (right) including growth factors (like fibroblast growth factor 21 [FGF21]), hormones (e.g., thyroid hormone [T3]), cytokines (e.g., interleukin 6 [IL6]) and factors that act in an autocrine or paracrine manner like adenosine and NO. NRG4 is a member of the EGF family of extracellular ligands that is enriched in brown adipocytes.

(B) NRG4 regulates de novo lipogenesis in hepatocytes via ErbB3/4 and STAT signaling. In addition, ErbB3 and ErbB4 might induce other cellular responses like proliferation.

BAT and liver as well as between brown adipocytes and neurons. The latter might enhance sympathetic innervation of WAT depots during browning (Rosell et al., 2014). Most importantly, Nrg4-dependent activation of ErbB3/4 might induce other cellular responses besides the regulation of hepatic lipogenesis. For instance, ErbB/HER receptors are known to induce a variety of cellular responses, such as mitogenesis. The ErbB3 receptor promotes cell survival, and amplification of this receptor has been reported for numerous cancers. Thus, activation of Nrg4/ErbB might have unwanted oncogenic effects in liver and other tissues (Figure 1B).

Overall, these novel results by Wang et al. (2014) demonstrate the importance of BAT for whole-body metabolism and highlight its endocrine functions. It will be interesting to explore the therapeutic relevance of the endocrine functions of BAT and whether Nrg4 can be used to treat NAFLD.

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